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(54) Title: TREATMENT OF COMPULSIVE BEHAVIOURS IN MAN AND ANIMALS

(57) Abstract

NMDA receptor antagonists can be used in methods of treatment, for reducing the frequency of stereotypic behaviors in animals and for reducing the frequency of analogous compulsive behaviours in humans, for example, those that have been said to be a manifestation of, or related to, obsessive-compulsive disorder. Of particular interest are the (+) enantiomers of opioid receptor binding compounds, which can reduce the frequency of the behaviours, while having no effects from binding at the opioid receptor.

No fat + fibre (+) antacid

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TREATMENT OF COMPULSIVE BEHAVIORS IN MAN AND ANIMALS

BACKGROUND OF THE INVENTION

Stereotypic behavior in animals (also called "repetitive" or "compulsive" behavior) has been defined by some researchers as acts that are repetitive and constant, which may appear to serve no obvious purpose, and may even be injurious. One of the most common of these behaviors is, for example, crib-biting by horses -- grabbing and biting of the feed bin or of parts of the structure in which the horse is housed (also called "cribbing" -- see US 4,692,451 for a description of this behavior, associated behaviors, and resulting problems). Another common behavior in dogs is compulsive licking of itself -- even to the point of aggravating a sore ("lick granuloma" or "acral lick"). Stereotypies may show some degree of variation, and may be unlike the more typical behaviors such as cribbing and licking, in that they have no features of repetitive motion, but are characterized rather by motionless staring or a frozen body position.

The repetitive behaviors of animals and the compulsive behaviors of humans have both responded to treatment with some of the same drugs. See, e.g., regarding treatment of acral lick with drugs that have shown benefit in human obsessive-compulsive disorder (OCD), Rapoport, J.L., *Clin. Neurophar. 15*:Suppl. 1 Pt

In another particular embodiment, the invention is a method for treating compulsive behaviors in dogs, such as compulsive licking (acral lick), tail chasing and whirling, pacing, fly chasing, shadow or light chasing, excessive barking, stone eating, excessive drinking, and excessive eating, comprising administering to the dog an effective amount of an NMDA receptor antagonist.

Also an embodiment of the invention is a method for treating compulsive behaviors in cats, such as wool sucking, compulsive licking, tail chasing, hoarding, pacing, excessive marking, compulsive masturbation, and compulsive aggression.

A further embodiment of the invention is a method for treating compulsive behaviors in birds, such as feather and skin picking.

The invention relates to a method for treating a disorder (or more than one disorder, as it is possible that two or more can occur together) in humans, variously termed repetitive, stereotypic, or compulsive behavior, and which can also be self-injurious, by administering to the human, by one or more appropriate routes and by appropriate doses, one or more NMDA receptor antagonists, thereby relieving the frequency and/or intensity of the compulsion and reducing the frequency and/or intensity of the behavior.

Examples of the human behaviors which can be treated by these methods include, but are not limited to: obsessive-compulsive disorder (with its various manifestations of checking, counting, washing to remove contamination, etc.), trichotillomania, psychogenic excoriation, nail biting, compulsive exercising, smoking compulsion, drug (opioid) addiction, and alcohol addiction. These compulsive behaviors may be related also to compulsive gambling, compulsive shopping, and eating disorders.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 is a graph in which cumulative crib-bites per time after administration of D-methadone (diamonds), as well as the rate of crib-bites per 5-minute interval (squares) are plotted, showing the effect of D-methadone on the rate of compulsive crib-biting in horses.

The invention relates to methods of treating animals displaying various types of repetitive and/or compulsive (frequently also called stereotypic) behaviors using compounds that are characterizable as NMDA receptor antagonists (having specific binding activity to NMDA receptors and/or the ability to block activation of the NMDA ligand-gated channel by an activating compound).

Compulsive or stereotypic behaviors in dogs can be put into several categories. "Grooming behaviors" can include, for example, lick granuloma (acral lick), compulsively licking objects, self-scratching, chewing feet, hair and nails, etc., flank sucking and air licking. "Locomotory behaviors" can include, for example, running and jumping, pacing, head shaking, paw shaking, tail swishing, freezing, whirling, tail chasing, walking in a pattern, as along a fence, digging and floor scratching. "Vocalization behaviors" include, for example, rhythmic barking, growling or snarling at self, barking at food, crying and howling. "Predatory behaviors" include, for instance, staring, air batting, jaw snapping, pouncing, prey chasing or searching, ducking, and fly chasing. "Eating and drinking behaviors" include, for example, excessive drinking, polyphagia, excessive drooling, gravel and dirt eating, stone chewing, wool sucking, and eating fabrics. "Sexual behaviors" include, for example, compulsive mounting. See, for tables compiling the observed behaviors of not only cats and dogs, but also horses, primates and other species

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Dodman, N.H., "Veterinary Models of Obsessive-Compulsive Disorder," Chapter 16, pp. 319-334 In *Obsessive-Compulsive Disorders: Practical Management* (M.A. Jenike *et al.*, eds.), Moseby, Boston, 1998. See also N.H. Dodman et al., "Veterinary Models of OCD," Chapter 6, pp. 99-143, In *Obsessive-Compulsive Disorders: Diagnosis, Etiology and Treatment*, (E. Hollander *et al.*, eds.), Marcel Dekker, New York, 1997. See also Tables 1 and 2 in Luescher, U.A. *et al.*, "Stereotypic or Obsessive-Compulsive Disorders in Dogs and Cats," In *Veterinary Clinics of North America: Small Animal Practice 21(2)*:401-413 (March, 1991).

Cats can exhibit behaviors similar to those seen in dogs, with the most common behaviors being those related to grooming, such as excessive self-licking and hair chewing. Other repetitive behaviors are tail chasing, hoarding, wool

Stereotypic animal behaviors have been compared to obsessive-compulsive disorder and disorders involving similar repetitive or compulsive behaviors in humans. As Freud described compulsive behavior, "the patient is impelled to perform actions which not only afford him no pleasure but from which he is powerless to desist." It has been hypothesized that a more satisfactory definition of stereotypies or compulsive behaviors would encompass both the animal and human syndromes, by being based on common, specific neuropathologic differences in the brains of animals or humans manifesting these behaviors, compared to animals or humans that do not manifest such behaviors. See discussion in Luescher, U.A. *et al.*, "Stereotypic or Obsessive-Compulsive Disorders in Dogs and Cats," In *Veterinary Clinics of North America: Small Animal Practice 21(2)*:401-413 (March 1991).

The similarities have led some to refer to not only the human behaviors, but also the animal behaviors, as "compulsive" behaviors or "obsessive-compulsive disorders." See Overall, K.L., *Canine Practice 17*:39-42, 1992; Dodman, N.H. and B. Olivier, *CNS Spectrums 1(2)*:10-15, 1996. It has been proposed that acral lick in dogs, and compulsive bar biting and chain chewing of tethered sows, as well as several other behaviors of animals, might serve as useful models of human obsessive-compulsive disorder (Dodman, N.H. and B. Olivier, *CNS Spectrums 1(2)*:10-15, 1996). Compulsive self-grooming behaviors in animals, in particular, have been compared with trichotillomania in humans (Moon-Fanelli, A.A. et al., Chapter 3, pp. 63-92 In *Trichotillomania*, (D.J. Stein et al., eds.), American Psychiatric Press, Inc., Washington, D.C. The serotonin reuptake inhibitor citalopram has been found to be useful in the treatment of OCD and possibly compulsive hair-pulling in humans, and has been used successfully, in the majority of the dogs in the study reported, to treat acral lick dermatitis (Stein, D.J. *et al.*, *Depression and Anxiety 8*:39-42, 1998). These data provide evidence that acral lick dermatitis can be a useful animal analog of OCD.

Similarities that can be observed among the repetitive animal behaviors, and between the repetitive behaviors of animals and the repetitive behaviors of humans, suggest a common etiology. In addition, there are studies that link one human syndrome to another. Neurologic disorders such as epilepsy, Sydenham's chorea,

and are selectively activated by the artificial glutamate analog N-methyl-D-aspartate. There is evidence that NMDA receptors play an important role in learning and in other phenomena in the brain, such as drug dependence and addiction, chronic pain, and CNS development, as well as in normal or disturbed synaptic transmission in some areas of the CNS. See, for review on NMDA receptors, Danysz, W. and Parsons, C.G., *Pharmacological Reviews 50*(4):597-664, 1998.

An NMDA receptor antagonist is any one of a number of agents which has been shown to bind to NMDA receptors and/or block any of the sites that bind glycine, glutamate, NMDA or phencyclidine (PCP). Blocking the NMDA receptor sites has the effect of preventing the creation of an action potential in the cell. NMDA receptor antagonists include those compounds that preferentially bind to NMDA receptors, but may also have other activities.

NMDA receptor antagonists include the following: previously identified competitive and non-competitive antagonists of NMDA receptors, which may bind, for instance, at the glycine site (on the NR1 subunit) and/or at the glutamate recognition site (on the NR2 subunit). Preferred NMDA receptor antagonists are those that have the ability to cross the blood-brain barrier and also demonstrate a low incidence of side effects. Such NMDA receptor antagonists can include, for example, compounds known as arylcyclohexylamines such as the anesthetic ketamine, neuroleptics such as haloperidol (Coughenour, L.L. and J.J. Corden, *J. Pharmacol. Exp. Ther. 280*:584-592, 1997) and the anti-Parkinson drug amantadine. Ifenprodil and eliprodil are neuroprotective agents whose mechanism of action has been attributed to their NMDA antagonist properties (Scatton, B. *et al.*, pp. 139-154 *In* Direct and Allosteric Control of Glutamate Receptors, Palfreyman, M.G. et al., eds., CRC Press, 1994). Trifluperidol and haloperidol have been shown to have a similar selectivity for the NR1a/NR2B receptor subtype expressed in *Xenopus* oocytes (Ilyin, V. *et al., Soc. Neurosci. Abstracts 21*:835, 1995. Memantine, felbamate, ifenprodil, eliprodil, CGS19755, remacemide, and CNS 1102 are also antagonists of NMDA receptors (Lipton, S.A. and P.A. Rosenberg, *New England Journal of Medicine 330 (9)*:613-622, 1994). A large number of NMDA receptor antagonists have been synthesized and tested for interaction with the NMDA

Ther. 288:204-210 (1999) and in Blanpied, T.A. *et al., J. Neurophysiol. 77*:309-323 (1997), measuring current amplitudes on rat cortical neurons. Tests of the effectiveness of NMDA receptor antagonists as antinociceptive agents are the rat tail-flick test and the formalin test, both described in Shimoyama, N. *et al., J. Pharmacol. Exp. Ther. 283*:648-652 (1997). Other assays for NMDA receptor binding and effects of this binding are referred to in the review by Danysz and Parsons, *Pharmacological Reviews 50*(4):597-664, 1998.

Preferred NMDA receptor antagonists are those which have a K_D in an NMDA receptor binding assay greater than 10 μM and less than or equal to 100 μM, more preferred are those NMDA receptor antagonists which have a K_D greater than 1 μM and less than or equal to 10 μM, even more preferred are those NMDA receptor antagonists which have a K_D greater than 100 nM and less than or equal to 1 μM, still more preferred are those NMDA receptor antagonists which have a K_D greater than 10 nM and less than or equal to 100 nM, and most preferred are those NMDA receptor antagonists which have a K_D equal to or less than 10 nM.

There is evidence for three major categories of opioid receptors in the central nervous system. These have been designated μ, κ, and δ. Binding to the opioid receptors can be measured in assays such as those described in Kristensen, K. *et al., Life Sciences 55*(2):PL45-PL50 (1994), using bovine caudate nucleus. Opioid receptor binders (which act either as an agonist or antagonist) are those compounds that bind to opioid receptors with a dissociation constant of less than about 100 nM. Preferably, opioid receptor binding molecules bind to opioid receptors with a K_D of less than 10 nM. A given opioid drug may interact to a variable degree with all three types of receptors and act as an agonist, partial agonist, or antagonist, at each type of receptor. The antagonist naloxone binds with high but variable affinity to all of these receptors. The term "naloxone-sensitive" is sometimes used synonymously with "opioid" in describing the actions of a given compound. See Jaffe, J.H. and W.R. Martin, "Opioid Analgesics and Antagonists," pp. 485-521 In *The Pharmacological Basis of Therapeutics* (A.G. Gilman et al., eds.), 8th ed., Pergamon Press, New York, 1990.

necessary (e.g. oral surgery or other surgery), as (+) enantiomers of narcotic antagonists do not block narcotic analgesia. The (+) enantiomers, unlike some known NMDA antagonists, readily cross the blood brain barrier. They do not produce toxic side effects like dizocilpine (MK-801). There is much experience with dextromethrophan as an anti-tussive with very little toxicity. Furthermore, there is considerable experience in treating addiction with (-) naltrexone and with racemic methadone. Toxicity of these substances is minimal.

Substituting (+) methadone for racemic methadone or (-) acetyl-l methadol in the treatment of narcotic addicts would have many advantages, including: 1) decreased craving without maintaining addiction; 2) no tolerance, and therefore lower doses; 3) no problems with security or drug diversion; and 4) less difficulty in weaning addicts. Block of NMDA receptors should also decrease craving for cocaine and alcohol (Sass, H. *et al.*, *Arch. Gen. Psychiarty 53*:673-680, 1996; Mitchem, L.D. *et al.*, *Pharmacol. Biochem. Behavior 62*:97-102, 1999).

Preferred compounds to be used in the treatment of repetitive behavior disorders include (+) enantiomers of both natural and synthetic opioids, such as dextromethorphan, dextrorphan, (+) methadone and (+) pentazocine; (+) enantiomers of synthetic narcotic antagonists such as (+) naloxone, (+) naltrexone, (+) nalmefene, and (+) diprenorphine.

Compositions to be used in methods described herein for the treatment of stereotypic, self-injurious and compulsive behaviors in animals and in humans include those comprising NMDA receptor antagonists; those compositions comprising NMDA receptor antagonists, wherein the composition does not comprise haloperidol; those compositions comprising NMDA receptor antagonists, wherein the composition does not comprise haloperidol, and wherein the composition does not comprise primarily (-) enantiomer of an opioid receptor agonist or antagonist; compositions comprising NMDA receptor antagonists, wherein the composition does not comprise haloperidol, and wherein the composition does not comprise an opioid receptor agonist or antagonist as (-) or (+) enantiomer; also, compositions comprising a compound selected from the group consisting of: dextromethorphan, dextrorphan, naltrexone, naloxone, methadone, pentazocine, nalmefene,

Diagnostic and Statistical Manual of Mental Disorders (DSM-IV™), American Psychiatric Association, 1994.

Smoking compulsion in humans is the urge to perform the act of smoking (tobacco cigarettes, cigars, or tobacco contained in another vessel or vehicle). The act of smoking is the physical manipulation of the cigarette or other tobacco vehicle and the conscious control of breathing that is normally performed in the course of taking in and blowing out the tobacco smoke, primarily involving the hands and mouth, in a kind of ritual. Smoking compulsion usually accompanies the well-documented nicotine addiction resulting from frequent and habitual tobacco smoking, but can be thought of as a compulsion which is separate from the craving satisfied by the administration of nicotine by a route other than smoking. This compulsion to smoke may be responsible for the failure of the simple administration of decreasing doses of nicotine (by transdermal patch or by nicotine-containing chewing gum, for example) to wean smokers from their smoking habit.

Psychogenic excoriation (also sometimes referred to as neurotic excoriation or pathologic skin picking) is a human disorder characterized by excessive scratching, picking, gouging, or squeezing the skin, and occurs in approximately 2% of dermatology clinic patients, mostly female (Gupta, M.A. *et al., Compr. Psychiatry 27*:381-386, 1986). It has been hypothesized that psychogenic excoriation is an impulse control disorder which is related to obsessive-compulsive disorder, or which is a manifestation of obsessive-compulsive disorder (McElroy, S.L. *et al., J. Clin. Psychiatry 55*:33-53, 1994). Patients with psychogenic excoriation have responded to serotonin reuptake inhibitors such as fluoxetine and sertraline (Gupta, M.A. and A.K. Gupta, *Cutis 51*:386-387, 1993; Stein, D.J. *et al., Psychosomatics 34*:177-181, 1993; Phillips, K.A. and S.L. Taub, *Psychopharmacol. Bull. 31*:279-288, 1993; Kalivas, J. *et al., Arch. Dermatol. 132*:589-590, 1996). In a study of fluvoxamine (a selective serotonin reuptake inhibitor used in the treatment of OCD) for the treatment of psychogenic excoriation, patients showed significant improvement (Arnold, L.M. *et al., Journal of Clinical Psychopharmacology 19*:15-18, 1999).

In what can also be considered a related self-injurious behavior, scratching associated with pruritis has been shown to respond to peripherally acting opiates,

administered in any effective, convenient manner, including administration by topical, oral, anal, vaginal, intravenous, intraperitoneal, intramuscular, subcutaneous, intranasal, transdermal or intradermal routes, among others. In therapy or as a prophylactic, the active agent may be administered to a subject as an injectable composition, for example as a sterile aqueous dispersion, preferably isotonic, or "packaged" as liposomes or microspheres.

When injectable compositions are desired, the functional antagonists of the present invention may be formulated, for example, into preparations for injection by dissolving, suspending or emulsifying them in an aqueous or non-aqueous solvent, such as vegetable oil, synthetic aliphatic acid glycerides, esters of higher aliphatic acids or propylene glycol; and if desired, with conventional additives such as solubilizers, isotonic agents, suspending agents, emulsifying agents, stabilizers and preservatives.

Alternatively, if one wishes to prepare an oral dosage form containing one of the functional antagonists herein encompassed, commonly used and pharmaceutically acceptable tableting excipients, such as lactose, microcrystalline cellulose, corn starch, stearic acid, or the like, may be used, if desired, to prepare such dosage forms.

Alternatively, the composition may be formulated for topical application, for example, in the form of ointments, creams, lotions, eye ointments, eye drops, ear drops, mouthwash, impregnated dressings and sutures and aerosols, and may contain appropriate conventional additives, including, for example, preservatives, solvents to assist drug penetration, and emollients in ointments and creams. Such topical formulations may also contain compatible conventional carriers, for example cream or ointment bases, and ethanol or oleyl alcohol for lotions.

In addition, the amount of the compound will vary depending on the size, age, body weight, general health, sex, and diet of the host, and the time of administration, the biological half-life of the compound, and the particular characteristics and symptoms of the disorder to be treated. Adjustment and manipulation of established dose ranges are well within the ability of those of skill in the art, and preferably minimize side effects and toxicity.

Table 1

Effect of some Drug Treatments on the Rate of Crib Biting

Horse	Drug Dose & Route	Duration of Effect	Crib-biting Frequency number per minute	Number per minute
			Before treatment	After treatment
CB	(-) naloxone .04 mg/kg, i.v.	65 min. (10 min lag)	12	0.1
CB	(+) naloxone 0.12 mg/kg, i.v.	60 min. (30 min lag)	10	6.6
CB	(+) naloxone 0.18 mg/kg, i.v.	60 min. (no lag)	9.2	0.8
CB	Dextromethorphan 1.0 mg/kg, p.o.	90 min. (35 min lag)	8	1.7
CB	Dextromethorphan 1.0 mg/kg, i.v.	35 min (no lag)	7.6	0.3
CB	(+) Methadone 0.2 mg/kg, i.v.	20 min (10 min lag)	8.8	2.6
CB	(+) Methadone .01 mg/kg, i.v.	10 min	8.2	5.5
CB	ketamine 0.2 mg/kg, i.v.	50 min (no lag)	8.2	1.3
Frito	Dextromethorphan 3.2 mg/kg p.o.	100 min (30 min lag)	3.5	1.8
Full Circle (turning)	Dextromethorphan 1.0 mg/kg,. i.v.	45 min (no lag)	3.5 turns per min.	.3 turns per min.

Table 2: Effect of NMDA Blockers on Pruritus in Mouse: Blocker Administered 10 Minutes Before 48/80

Time	Cumulative Scratches		
Minutes	Control	Naltrexone 10 mg/kg	Dextromethorphan 10 mg/kg
10	5	0	1
20	52	0	57
30	166	0	105
40	277	1	157
50	364	61	182
60	498	73	192
Time	(+) methadone 10 mg/kg		Control
10	0		3
20	0		79
30	0		99
40	0		227
50	0		404
60	0		456

All references cited herein not previously specifically stated as being incorporated by reference are hereby incorporated by reference in their entirety.

While this invention has been particularly shown and described with references to preferred embodiments thereof, it will be understood by those skilled in the art that various changes in form and details may be made therein without departing from the spirit and scope of the invention as defined by the appended claims.

consisting of: cribbing, wind sucking, stall walking, weaving, head bobbing, pawing, tonguing, self-biting, and head shaking.

5. A method for treating a repetitive behavior disorder in an animal, comprising administering to the animal an effective amount of a composition comprising a compound selected from the group consisting of: dextromethorphan, dextrorphan, naltrexone, naloxone, methadone, pentazocine, nalmefene, diprenorphine, nalorphine, hydromorphone, oxymorphone, hydrocodone, oxycodone, buprenorphine, butorphanol, nalbuphine, fentanyl, metazocine, cyclazocine, etazocine, and a combination of any of the preceding, wherein the compounds are predominantly (+) enantiomer.

6. A method for treating a repetitive behavior disorder in a dog, comprising administering to the dog an effective amount of a composition comprising one or more NMDA receptor antagonists, wherein the composition does not comprise haloperidol, and wherein the composition does not comprise primarily (-) enantiomer of an opioid receptor agonist or antagonist.

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7. A method for treating a repetitive behavior disorder in a dog, comprising administering to the dog an effective amount of a composition comprising one or more NMDA receptor antagonists, wherein the composition does not comprise haloperidol, and wherein the composition does not comprise an opioid receptor agonist or antagonist as (-) or (+) enantiomer.

8. A method for treating a repetitive behavior disorder in a dog, comprising administering to the dog an effective amount of a composition comprising one or more NMDA receptor antagonists, wherein the composition does not comprise haloperidol, and wherein the composition does not comprise

13. A method for treating stall walking in an animal of an equine species, comprising administering to the animal an effective amount of a composition comprising one or more NMDA receptor antagonists, wherein the composition does not comprise primarily (-) enantiomer of an opioid receptor agonist or antagonist.

14. A method for treating stall walking in an animal of an equine species, comprising administering to the animal an effective amount of a composition comprising one or more NMDA receptor antagonists, wherein the composition does not comprise haloperidol, and wherein the composition does not comprise primarily (-) enantiomer of an opioid receptor agonist or antagonist..

15. A method for treating stall walking in an animal of an equine species, comprising administering to the animal an effective amount of a composition comprising one or more NMDA receptor antagonists, wherein the composition does not comprise haloperidol, and wherein the composition does not comprise an opioid receptor agonist or antagonist as (-) or (+) enantiomer.

16. A method for treating stall walking in an animal of an equine species, comprising administering to the animal an effective amount of a composition comprising one or more NMDA receptor antagonists, wherein the composition does not comprise an opioid receptor agonist or antagonist.

17. A method for treating stall walking in an animal of an equine species, comprising administering to the animal an effective amount of a composition comprising one or more NMDA receptor antagonists,

23. A method for treating scratching associated with pruritis in an animal, comprising administering to the animal an effective amount of a composition comprising a compound selected from the group consisting of: dextromethorphan, dextrorphan, naltrexone, naloxone, methadone, pentazocine, nalmefene, diprenorphine, nalorphine, hydromorphone, oxymorphone, hydrocodone, oxycodone, buprenorphine, butorphanol, nalbuphine, fentanyl, metazocine, cyclazocine, etazocine, and a combination of any of the preceding, wherein the compounds are predominantly (+) enantiomer.

24. A method for treating obsessive-compulsive disorder in a human, comprising administering to the human an effective amount of a composition comprising one or more NMDA receptor antagonists.

25. A method for treating obsessive-compulsive disorder in a human, comprising administering to the human an effective amount of a composition comprising one or more NMDA receptor antagonists, wherein the composition does not comprise primarily (-) enantiomer of an opioid receptor agonist or antagonist.

26. A method for treating obsessive-compulsive disorder in a human, comprising administering to the human an effective amount of a composition comprising one or more NMDA receptor antagonists, wherein the composition does not comprise an opioid receptor agonist or antagonist as (-) or (+) enantiomer.

27. A method for treating obsessive-compulsive disorder in a human, comprising administering to the human an effective amount of a composition comprising one or more compounds selected from the group consisting of: dextromethorphan, dextrorphan, naltrexone, naloxone,

oxymorphone, hydrocodone, oxycodone, buprenorphine, butorphanol, nalbuphine, fentanyl, metazocine, cyclazocine, etazocine, and a combination of any of the preceding, wherein the compounds are predominantly (+) enantiomer.

32. A method for treating trichotillomania in a human, comprising administering to the human an effective amount of a composition comprising one or more NMDA receptor antagonists, wherein the composition does not comprise haloperidol.

33. A method for treating trichotillomania in a human, comprising administering to the human an effective amount of a composition comprising one or more NMDA receptor antagonists, wherein the composition does not comprise haloperidol and does not comprise an opioid agonist or antagonist as (-) or (+) enantiomer.

34. A method for treating trichotillomania in a human, comprising administering to the human an effective amount of a composition comprising a compound selected from the group consisting of: dextromethorphan, dextrorphan, naltrexone, naloxone, methadone, pentazocine, nalmefene, diprenorphine, nalorphine, hydromorphone, oxymorphone, hydrocodone, oxycodone, buprenorphine, butorphanol, nalbuphine, fentanyl, metazocine, cyclazocine, etazocine, and a combination of any of the preceding, wherein the compounds are predominantly (+) enantiomer.

35. A method for treating stereotypic movement disorder in a human, comprising administering to the human an effective amount of a composition comprising one or more NMDA receptor antagonists.

40. A method for treating smoking compulsion in a human, comprising administering to the human an effective amount of a composition comprising one or more NMDA receptor antagonists.

41. A method for treating smoking compulsion in a human, comprising administering to the human an effective amount of a composition comprising one or more NMDA receptor antagonists, wherein the NMDA receptor antagonist is not an opioid receptor agonist or antagonist.

42. A method for treating smoking compulsion in a human, comprising administering to the human an effective amount of a composition comprising a compound selected from the group consisting of: dextromethorphan, dextrorphan, naltrexone, naloxone, methadone, pentazocine, nalmefene, diprenorphine, nalorphine, hydromorphone, oxymorphone, hydrocodone, oxycodone, buprenorphine, butorphanol, nalbuphine, fentanyl, metazocine, cyclazocine, etazocine, and a combination of any of the preceding, wherein the compounds are predominantly (+) enantiomer.

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43. A method for treating psychogenic excoriation in a human, comprising administering to the human an effective amount of a composition comprising one or more NMDA receptor antagonists, wherein the composition does not comprise (-) naltrexone.

44. A method for treating psychogenic excoriation in a human, comprising administering to the human an effective amount of a composition comprising a compound selected from the group consisting of: dextromethorphan, dextrorphan, naltrexone, naloxone, methadone, pentazocine, nalmefene, diprenorphine, nalorphine, hydromorphone,

48. A method for treating scratching associated with pruritis in a human, comprising administering to the human an effective amount of a composition comprising one or more NMDA receptor antagonists, wherein the composition does not comprise (-) naloxone.

49. A method for treating scratching associated with pruritis in a human, comprising administering to the human an effective amount of a composition comprising a compound selected from the group consisting of: dextromethorphan, dextrorphan, naltrexone, naloxone, methadone, pentazocine, nalmefene, diprenorphine, nalorphine, hydromorphone, oxymorphone, hydrocodone, oxycodone, buprenorphine, butorphanol, nalbuphine, fentanyl, metazocine, cyclazocine, etazocine, and a combination of any of the preceding, wherein the compounds are predominantly (+) enantiomer.

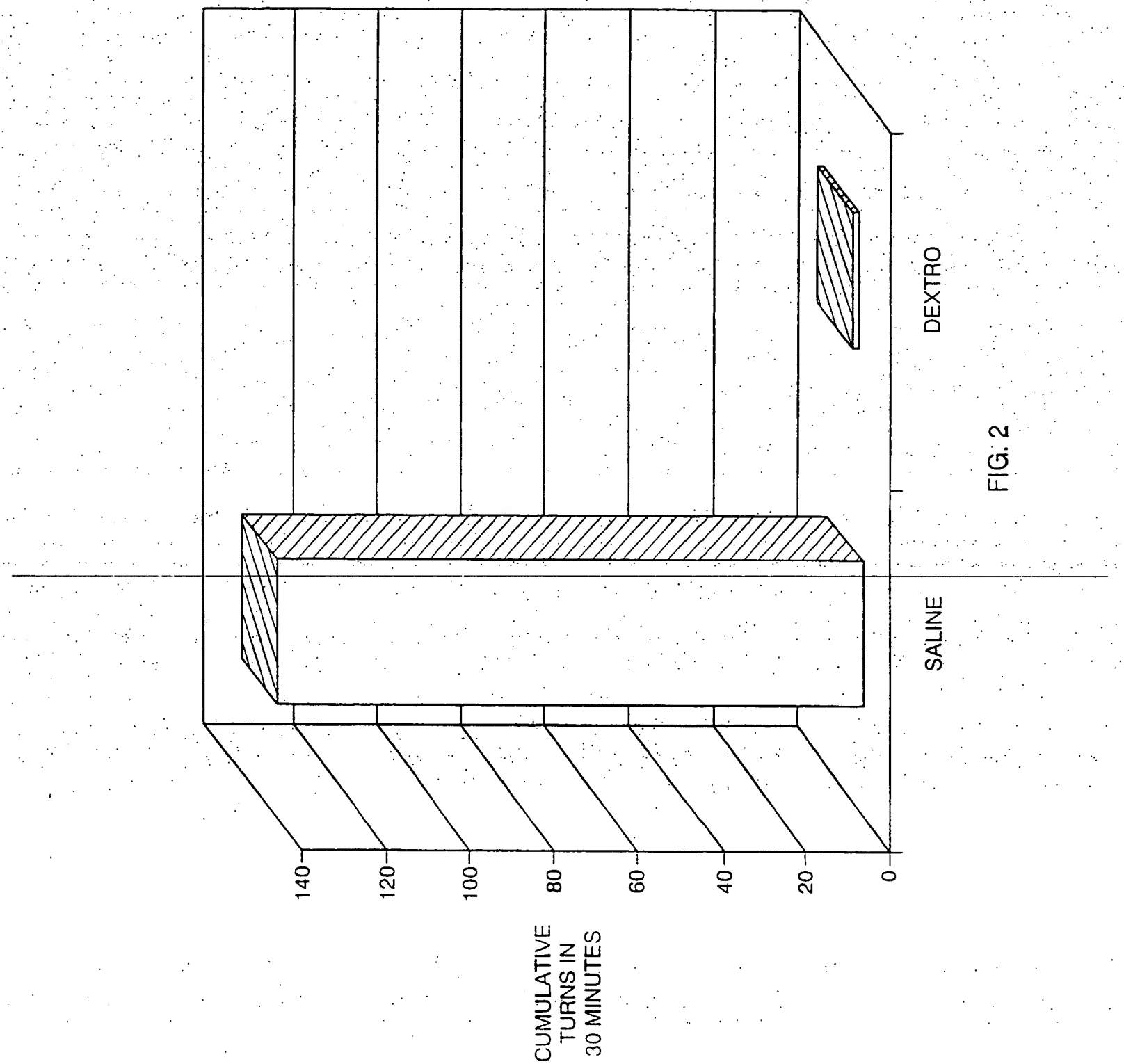
DEXTRO
SALINE
CUMULATIVE TURNS IN 30 MINUTES
140
120
100
80
60
40
20
0

FIG. 2

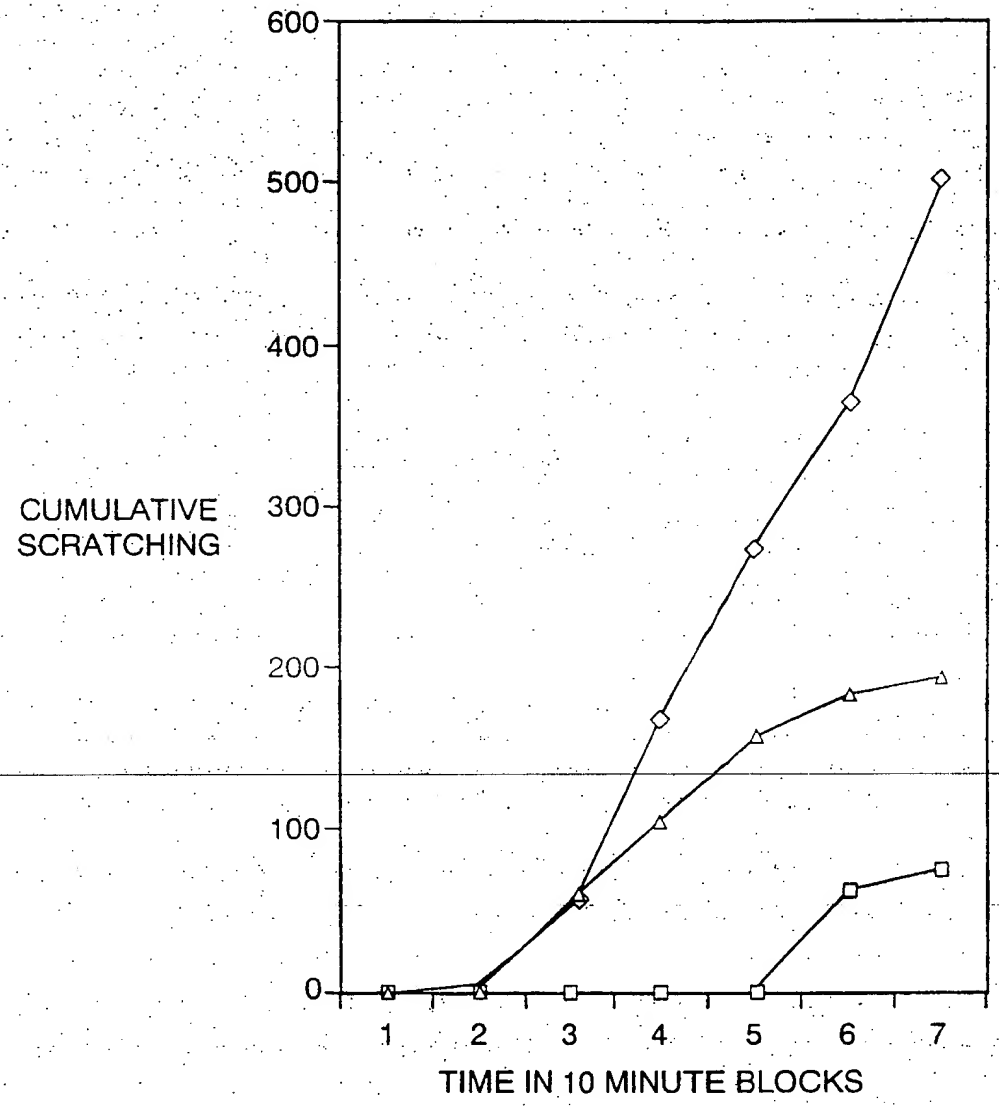
600
500
400
300
200
100
0
CUMULATIVE SCRATCHING
1
2
3
4
5
6
7
TIME IN 10 MINUTE BLOCKS

FIG. 4

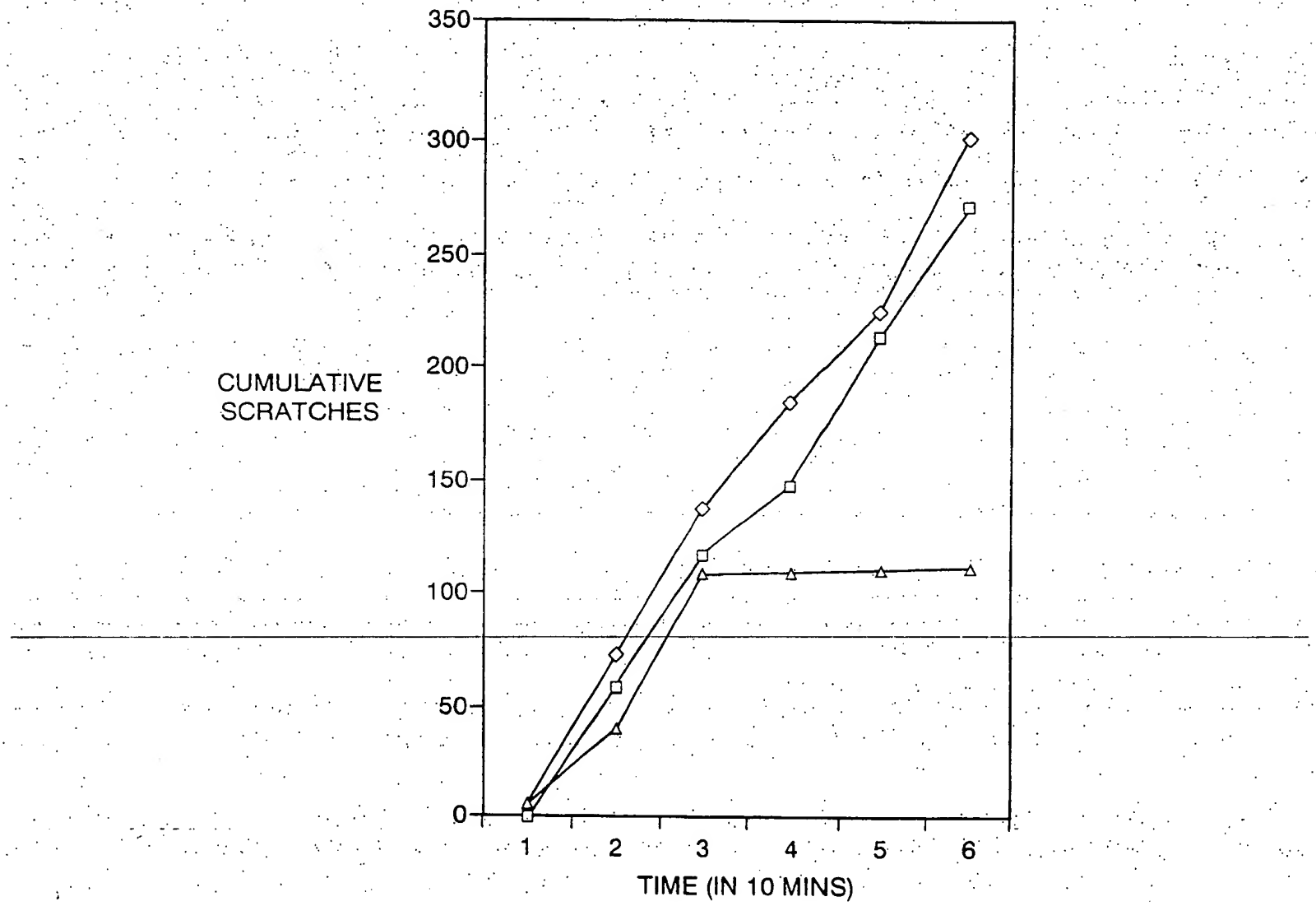
350
300
250
200
150
100
50
0
CUMULATIVE SCRATCHES
1
2
3
4
5
6
TIME (IN 10 MINS)

FIG. 5B

INTERNATIONAL SEARCH REPORT

Inte...ational Application No
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category '	Citation of document, with indication where appropriate, of the relevant passages	Relevant to claim No.
X	US 4 692 451 A (DODMAN NICHOLAS H ET AL) 8 September 1987 (1987-09-08) cited in the application claims 2,3	1-5, 9-11, 13-15
X	WO 97 33581 A (KRISHNAN SARIN SUCHITRA ;UNIV YALE (US); MEANDZIJA BORIS (US); CON) 18 September 1997 (1997-09-18) page 5, line 18 - line 26	1,24,25
X	KOYUNCUOGLU ET AL: "the treatment of heroin addicts with dextromethorphan " INT. J. CLIN. PHARMACOL. THER. TOXICOL., vol. 28, no. 4, 1990, pages 147-152, XP002112203 abstract page 151, right-hand column	1,2,5, 24-27,46
X	WELCH ET AL: "the treatment of a chronic organic mental disorder with dextromethorphan in a man with severe mental retardation" BR. J. PSYCHIATRY, vol. 161, 1992, pages 118-120, XP002112204 abstract	1,2, 24-27
X	POMERLEAU O.F.: "endogenous opioids and smoking: a review of progress and problems " PSYCHONEUROENDOCRINOLOGY, vol. 23, no. 2, February 1998 (1998-02), pages 115-130, XP002112205	1,24,25
A	abstract page 126, paragraph 2	40-42
X	SMITH ET AL: "naltrexone for neurotic excoriations" J. AM. ACAD. DERMATOL., vol. 20, no. 5, 1989, pages 860-861, XP002112206 cited in the application	22,24, 47,48
A	the whole document	1,2
X	DODMAN ET AL: "use of narcotic antagonists to modify stereotypic self-licking self-chewing and scratching behavior in dogs" J. AM. VET. MED. ASSOC., vol. 193, no. 7, 1988, pages 815-819, XP002112207 cited in the application abstract	1,6,19, 22

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INTERNATIONAL SEARCH REPORT

Int. ..ional Application No
PCT/US 99/04680

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WOODS-KETTELBERGER ET AL: "animal models with potential applications for screening compounds for the treatment of obsessive-compulsive disorders" EXPERT OPIN. INVEST. DRUGS, vol. 6, no. 10, 1997, pages 1369-1381, XP002112214 the whole document ---	1-49
A	GHAZIUDDIN ET AL: "haloperidol treatment of trichotillomania in a boy with autism and mental retardation" J. AUTISM AND DEVELOPMENTAL DISORDERS, vol. 21, no. 3, 1991, pages 365-371, XP002112215 the whole document -----	32-34

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Present claims 1-4, 6-11, 13-17, 19, 20, 22, 24-26, 28-30, 32, 33, 35-38, 40, 41, 43 , 47 and 48 relate to an extremely large number of possible compounds. Support within the meaning of Article 6 PCT and disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts relating to the compounds mentioned in claims 5, 12, 18, 21, 23, 27, 29, 34, 39, 42 to 46 and 49.

The applicant's att..tion is drawn to the fact that claims relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.